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Variant classification and interpretation

Workshop report

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Authors:

Sobia Raza, Leila Luheshi, Alison Hall, Emma Baple, Sian Ellard, Dominic McMullan

Acknowledgements:

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Published by PHG Foundation
2 Worts Causeway
Cambridge
CB1 8RN
UK

Tel: +44 (0) 1223 761 900

Correspondence to:

sobia.raza@phgfoundation.org
bsgm@bsgm.org.uk

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1. Introduction and background

1.1. The workshop

This report summarises a meeting held on 4 November 2016 to discuss guidelines for the classification and interpretation of genomic variants in the context of rare diseases. The meeting was jointly hosted by the Association for Clinical Genomic Science (ACGS), the British Society for Genetic Medicine (BSGM), and the Genomics England core Validation and Feedback GeCIP (Genomics England Clinical Interpretation Partnership) group.

Aim of the meeting: To reach national consensus on the principles that should underpin the development of variant classification and interpretation guidelines for use within the UK clinical genomics community; specifically considering whether and how the American College of Medical Genetics and Genomics (ACMG) sequence variant guidelines should be adopted and implemented.

Participants: Representatives were invited from all UK Regional Genetic Centres, as well as the BSGM (and constituent groups), Genomics England, NHS-England, UKGTN, UK NEQAS, the DECIPHER/DDD project, and the PHG Foundation (see Appendix 5.2 for further delegate details).

Meeting format: The workshop consisted of two sets of invited presentations (Appendix 5.3) followed by focus group discussions to consider aspects around the identification, establishment, adoption and revision of variant classification guidelines. The two sessions of the meeting considered:

- The experience to date of the ACMG Guidelines and whether/how this framework could be applied within the UK
- How a common variant interpretation framework could be enhanced, particularly to better integrate the practice of laboratory and clinical genomic medicine

This report summarises the key themes arising from the presentations and discussions in these two sessions, including the challenges, the potential solutions, and areas of consensus.

1.2. The role of guidelines in supporting consistent variant classification practice

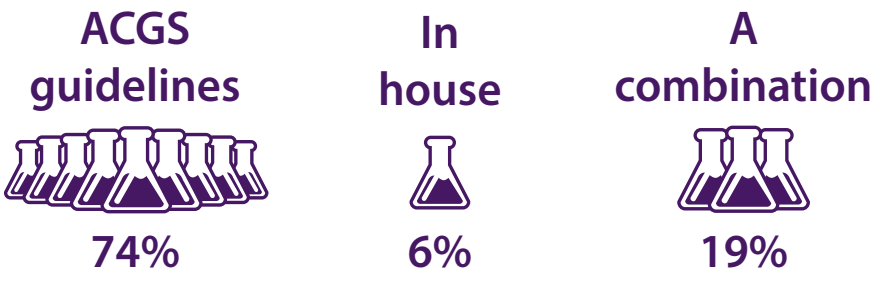
The interpretation and classification of sequence variants entails the collation and evaluation of various sources of evidence to determine the clinical significance of variants identified through diagnostic testing for a disease with a suspected underlying genetic cause. Together with other clinical information, the variant interpretation may be used to inform the clinical management of a patient and possibly their relatives.

The ability of all NHS genetics laboratories to reach a consistent and accurate interpretation of a particular variant is paramount given the implications for patient management and safety. Key to driving this consistency is the use of a common set of principles and approach to assessing variants, alongside closer working with clinical colleagues enabling more comprehensive consideration of clinical phenotypes when determining the likely pathogenicity of sequence variants.

A survey circulated ahead of the workshop indicated that currently most NHS clinical genetic laboratories apply the ACGS guidelines[1] (published in 2013) for evaluating sequence variants [23 of 31 survey respondents (74%)], whilst others [6 of 31 (19%)] use a combination of ACGS guidelines along with other in-house classification systems or external guidelines (Appendix 5.4). However, differences in classification persist (see 1.3). Given the rapid increase in the number of novel variants and genes being analysed through genomic testing, there is an urgent need to revise the current ACGS interpretation guidelines to ensure greater consistency can be achieved as complexity also increases.

> The ability of all NHS genetics laboratories to reach a consistent and accurate interpretation of a particular variant is paramount given the potential implications for patient management and safety...As the complexity of analysis increases, there is a particularly urgent need to revise the current ACGS interpretation guidelines to achieve greater consistency.

Which guidelines do laboratories use to evaluate sequence variants?



1.3. NEQAS variant classification experiences

First introduced in 2012, the NEQAS external quality assessment (EQA) scheme for variant interpretation provides laboratories with data on variants and requests that laboratories classify them according to the ACGS five-point scale. Annual assessments from 2012–2016 have demonstrated a degree of disparity in the interpretation of variants; in some cases, classification of the same variant ranged from class 2 (likely benign) to class 5 (pathogenic). Interpretations have varied even when the assessment is confined to genes/conditions with which the laboratories have experience (e.g. cardiomyopathies).

The 2016 assessment was distributed to clinicians – who were also asked to comment on whether the interpretations would be used for clinical management – and to laboratory scientists. In general there was consistency between the interpretations reached by the clinician and laboratory groups, with the clinicians tending to classify variants slightly higher than the clinical scientists. However, there was some variability across the country in the interpretation of some variants. There was clear agreement that only pathogenic and (some) likely pathogenic variants would be used to inform clinical management.

1.4. The ACMG and AMP guidelines for variant interpretation

In 2015 the ACMG in collaboration with the Association for Molecular Pathology (AMP) published guidelines[2] to enable a more systematic approach to variant interpretation for Mendelian (monogenic) disease diagnosis.

The ACMG framework details different levels of evidence for or against pathogenicity and outlines rules for combining evidence sets in order to classify variants into one of five categories. The guidelines were developed by a group of clinicians and laboratory representatives – with considerable community input – through workshops, literature evaluation, surveys, testing and feedback.

In the United States the guidelines have been widely adopted by clinical laboratories, integrated into a number of commercial analysis platforms, and used to resolve differences in the classification of variants in the NCBI ClinVar database. Many presentations at the European Society of Human Genetics meeting in Barcelona 2016 also highlighted wide adoption of the guidelines in Europe.

2. Experiences of implementing and applying ACMG Guidelines

The 4 November meeting considered whether, given the trend towards their global adoption, the ACMG Guidelines applied in the UK context, could improve the quality and consistency of variant interpretations. Invited presenters (Appendix 5.3) shared their experience of implementing or testing the ACMG Guidelines in their laboratory or disease domain. Focus group discussions further explored issues relating to the adoption of the ACMG Guidelines within UK genomic services.

2.1. What has the experience of the ACMG Guidelines been to date?

At least two published US-based evaluations of the ACMG Guidelines have broadly supported their use as a mechanism to drive consistency and improvement in quality of variant interpretation. One pilot assessment across nine laboratories in the United States found that although use of the guidelines did not initially improve inter-laboratory concordance of variant classifications, they did provide a valuable common framework for subsequent discussion of evidence and resolution of classification differences; consequently improving inter-laboratory concordance from 34% to 71%[3]. The authors noted that the resolution of differences would have been more difficult if each laboratory had relied on an independent method for variant assessment[3].

A separate evaluation, specifically in the context of inherited breast cancer susceptibility, supported the clinical utility of the guidelines, but highlighted that they do not eliminate the requirement for expert judgement in variant classification, and also found that automated variant interpretation is currently not ready for use in clinical practice[4]. For example, in their study, 182 of 306 variants identified as pathogenic, likely pathogenic or variants of uncertain significance (VUS) were revised following detailed manual analysis[4].

The UK experience of the ACMG Guidelines

The conclusions of these published evaluations were echoed by the UK genetics centres who had tested the ACMG Guidelines. Overall the guidelines provide a constructive and objective framework for assessing pathogenicity, however professional judgement remains essential to the interpretation process – particularly the input of disease and/or gene based expertise. For example, on assessment a professional may choose to override the conclusion that the strict application of the guidelines would lead to, and it remains a matter of judgement in some cases whether or not a particular evidence criterion applies or the level of weighting the evidence set carries. Indeed, the ACMG Guidelines do acknowledge the importance of applying professional judgement to the specific circumstances presented, and provide scope for flexibility in assessing evidence.

Specific challenges encountered in applying certain evidence criteria include:

- Overly stringent criteria applied to assessing the significance of the clinical phenotype (ACMG – PP4 criteria, the use of this criteria is limited to where there is a single genetic aetiology underlying a disorder)
- The issue around confirming maternity and paternity to obtain stronger evidence for an apparently *de novo* variant. This is not common practice in the UK

There are also gaps or limited guidance on:

- The use of evidence derived *in silico*
- Incorporation of functional evidence e.g. using data from MRI scans and loss of heterozygosity in tumour samples, where the results are pathognomonic of a specific single genetic cause of a disorder

The need to exercise professional judgement when assessing these evidence sets, and to take account of these issues in informing future improvements to the interpretation framework, was noted.

2.2. Should the ACMG Guidelines be adopted in the UK?

There was broad agreement that the UK clinical genomics community should adopt the ACMG Guidelines. Factors underpinning this consensus included the:

- Extensive development and testing process undertaken by the ACMG and AMP in devising the guidelines
- Broadly positive experience of the guidelines to date, with the scope for further refinement, and customisation (on a disease/gene basis) to improve and enhance them
- Benefits of UK harmonisation with the ACMG approach for promoting international consistency and facilitating the exchange of variant classifications

Moreover, since publication of the guidelines, tools and resources to help enhance application are being developed, including:

- A quantitative approach to assessing family co-segregation evidence[5]
- A framework for frequency-based filtering of candidate disease-causing variants[6]
- A web-tool to support ACMG pathogenicity calculations based on supplied evidence[7]

2.3. Potential challenges to the adoption and implementation of the ACMG Guidelines

In addition to the specific issues with individual evidence criteria that might require refinement as the guidelines evolve, delegates highlighted several practical challenges to implementing them in the UK context.

Will the guidelines result in more conservative calling?

Some queried whether the ACMG criteria could result in more conservative variant calling than current processes, and the impact this may have on result reporting and clinical practice. One presenting laboratory had compared the ACMG framework to their in-house interpretation process; of 40 previously classified variants, reassessed using ACMG Guidelines, 27 classifications were concordant with previous results, but 10 classifications were downgraded from pathogenic (3) or likely pathogenic (7) to uncertain significance and no variants were upgraded.

Will the guidelines potentially be more time consuming to apply during variant interpretation?

Whilst there were concerns as to whether the ACMG Guidelines would take longer to apply, the experience of some early adopters was that – as with current guidelines – the time taken to classify a variant generally depended on the degree of evidence required to inform the interpretation rather than the classification scheme being used.

How to determine and ensure the guidelines are driving consistency?

Beyond the adoption of the guidelines, additional mechanisms to ensure and support adherence and consistent application of the guidelines (such as training, EQA, sharing classifications – see 2.4) were viewed as crucial, especially as access to and/or use of tools and resources for variant assessment can differ between NHS Trusts. Since the ultimate objective of adopting the guidelines is to improve the quality and inter-laboratory consistency of variant interpretations, the importance of systems for evaluating consistency and quality was stressed.

2.4. Facilitating the UK implementation of the ACMG Guidelines

Processes and solutions for addressing some of the challenges identified and for expediting the effective implementation of the ACMG Guidelines across UK genomics services were explored.

Disease/gene based refinement of the ACMG Guidelines

There was recognition of the need to refine the guidelines on a gene/disease basis and to harmonise where possible with international developments. For example, in familial cancer, the majority of analysis is centred on 'common' phenotypes, and delegates had encountered challenges in applying the ACMG Guidelines, which in their current form work more effectively for rare conditions. In the United States, expert panels are being formed as part of the ClinGen resource consortium to develop gene and disease specific criteria to supplement the original ACMG Guidelines. UK coordination and dialogue with these groups was seen as an important step in understanding how sector specific guidelines are evolving in specific gene/disease domains and in informing UK developments.

Training and EQA

Training was not only viewed as an important mechanism to catalyse adoption of the guidelines, but also as an opportunity to identify UK specific issues, promote consistency in the application of the guidelines, and help facilitate their time efficient application. Multidisciplinary training for trainers on the classification system and an EQA scheme for measuring consistency were highlighted as necessary processes for encouraging and dispersing good practice.

Greater community collaboration and sharing of variant interpretations

The effectiveness with which the guidelines can drive consistency is especially contingent on the extent of collaboration and interaction between centres. Effective and consistent use of the guidelines can be augmented through sharing information on:

- The use of *in silico* tools/resources
- The degree of flexibility being adopted for specific evidence criteria and within specific disease/gene domains
- The decision processes underpinning variant classifications

There was strong agreement that a system for sharing [ACMG] variant interpretations (and potentially multidisciplinary team (MDT) reports) into a common agreed database (or infrastructure) would augment consistency of classifications. Support for the collection of familial cancer susceptibility data for Public Health England's (PHE) registries was encouraged, given the potential to help improve the understanding of variants through the linkage of genetic data to longitudinal clinical/outcome data.

There was strong agreement that a system for sharing [ACMG] variant interpretations... into a common agreed database (or infrastructure) would augment consistency of classifications.

Communicating the UK approach to ACMG implementation

As tools, resources, and additional guidance to supplement the ACMG framework emerge, it will be crucial to communicate developments to the UK clinical genomics community through professional/scientific meetings, and also capture any changes in a unified UK best practice framework for variant interpretation. The need for incorporating minimal standards for recording and reporting decisions into any UK specific guidance was also underscored, including the harmonisation of terminology. For example, while the ACGM and HGVS have recommended removing the word 'mutation' and replacing with 'pathogenic variant' in descriptions of internal findings on clinical reports, in the UK there are conflicting views on this position (Appendix 5.4) and it was felt that further views needed to be sought, particularly from patient groups.

Does your laboratory agree with replacing 'mutation' with 'pathogenic variant' in internal reports?

Do not agree

32%

No, due to logistics

25%

Only *de novo* variants

7%

Agree

36%

3. Building-on the ACMG Guidelines

Having established a consensus for UK adoption of the ACMG Guidelines, the next session of the meeting considered how the guidelines might be enhanced to further support clinical practice in the UK.

In contrast to some other health systems, there is a high degree of laboratory and clinical integration in UK genetics/genomics services, but also a range of approaches to working across different NHS Trusts. Across these different models of service delivery, the clinical interpretation of variants – i.e. their contribution to a patient's phenotype – might predominantly be undertaken by the laboratory scientists, or predominantly by the referring clinicians, or collaboratively by MDTs comprising clinical scientists, and relevant clinicians (e.g. clinical geneticists, and/or disease specialists). As the complexity of genomic testing is increasing with the advent of large panels and exome and whole genome sequencing, so is the frequency of MDT working – in either physical, or virtual forums. Given this increasing clinician/laboratory scientist working and the integrated nature of current genetic services in the UK, delegates considered how the ACMG Guidelines could be enhanced – particularly to support the clinical interpretation of variants – within the UK context.

3.1. How could the guidelines be developed to support clinical practice?

The ACMG Guidelines provide a foundation for more systematic variant interpretations. However, there are two additional dimensions that could be added to make them more powerful and to unify the practice of laboratory and clinical genomic medicine.

Aligning guidance for all types of variants

There was consensus around the desire to establish a unified (single) set of guidelines that apply to all types of variants i.e. structural or single nucleotide variant (SNV) that may underpin rare disease. Currently the 2011[8] ACMG Guidelines for copy number variant (CNV) interpretation are the most widely adopted[9] guidance for structural variation. However, since the 2011 publication there have been a number of developments – including the convergence of genetic testing on the use of a single technology, and the increasing interpretation of CNVs in the context of known SNVs or indels (and vice versa). These developments are now driving considerations to harmonise the classification terminology applied to CNVs and SNVs; ideally towards the adoption of a consistent five tier classification system for all variants.

The ACMG are developing updated and platform agnostic CNV interpretation guidelines together with the ClinGen Structural Variation Interpretation Working group.

The ACMG are developing updated and platform agnostic CNV interpretation guidelines together with the ClinGen Structural Variation Interpretation Working group. A draft framework for scoring CNV microdeletions is being extensively road tested by the ClinGen laboratory consortium, with the opportunity for the ACGS to participate as a country 'naïve' to the framework's development. The completed guidelines – also including a framework including CNV duplications – are expected in 2017.

Integrating phenotype and clinical data

To determine whether a variant is contributing to the patient's phenotype requires an assessment of the variant interpretation in the context of the patient's clinical and phenotypic data (clinical-level interpretation). In their current form the ACMG Guidelines largely focus on 'variant-level' interpretation with limited guidance on relative contribution of phenotype to overall classification. Given the integrated nature of UK genomic services, a model for combining patient phenotypic and clinical data together with the variant interpretation, prior to the reporting of results could enhance the utility of the guidelines in the UK context.

Performing high-quality combined clinical and variant level interpretations, would help to better inform patient care – i.e. understand the significance and/or clinical implications of the genetic test results in the patient. Currently there is not a systematic and standardised process for phenotype capture, although models are being developed through the work of the 100,000 Genomes Project.

Moreover, practice for collating and integrating phenotypic and clinical data with the variant interpretation is varied and can be dictated by where clinical interpretation takes place and in what disease specialism (e.g. by the referring clinician, laboratory, or MDT). A laboratory may request clinical and phenotype data at the test referral stage, or prior to the reporting of results. In other cases the data may only be known and used by the referring clinician, or it might be collated and shared between a MDT.

3.2. What is required to support integrated genotype-phenotype interpretations?

Systems to collate and integrate genotype – phenotype data, and to facilitate laboratory – clinical interactions

In order to undertake combined variant and clinical-level interpretation in a patient context and to achieve consistent practices, standardised systems and processes to capture and collate clinical and phenotypic data – ideally upstream of the interpretation stage – will be required. Other than assisting the combined variant and clinical-level interpretation, using these types of systems enables a clearer audit trail and therefore more transparency – indirectly promoting public trust. The DECIPHER platform was presented as one way of achieving this.

First established in 2004 the principal functionality of DECIPHER is to support the deposition, up-to-date interpretation, and sharing of data. A recent release of DECIPHER (v9.11 – 2 November 2016), now supports implementation of the ACMG Guidelines. Using the 'pathogenicity module', evidence for/against a variant's pathogenicity can be recorded against the ACMG criteria, and an algorithmic calculation applied to classify a variant based on collated evidence. Accordingly, the terminology for variant classifications has been updated to be in line with the five-tier ACMG system.

A similar structured approach for recording clinical and phenotype data (a 'summative clinical assessment tool') has been developed by Dr Helen Firth following the workshop supporting the systematic evaluation of whether a variant explains clinical features (v9.13 - 22 February 2017). Additionally, this companion module could support MDT working in real time, and provide a visible trail of decision making, available in formats suitable for export and sharing.

Engagement with other clinical specialities

To ensure consistent practice across services in supporting integrated genotype-phenotype interpretations, it will be important to ensure the necessary phenotypic and clinical data can be collated regardless of the type of disorder and from where the patient's test has been referred. Referrals by 'mainstream' (non-genetics) clinical specialities may pose challenges to this data collation and integrated-interpretation process, as well as to the reporting of results. This is because many mainstream specialities may have less knowledge of the genetic testing process, and in contrast to clinical genetics, may typically have more distant relationships with genetics laboratories and more limited time per patient to collate the clinical and phenotypic data.

Addressing these challenges will require balancing the needs of the laboratory with those of the clinicians during the referral and interpretation process in order to:

- Obtain sufficient yet proportionate levels of clinical and phenotypic data to inform test choice and aid interpretation
- Ensure test reports are appropriately formatted and written for referring clinicians from a wide range of disciplines and who may have a variable level of understanding of clinical genetics so that the reports are understood and actioned appropriately

Dialogue and connection with existing mainstreaming genomics initiatives is one route to exploring these issues and identifying principles of best practice.

Data sharing

Improving the consistency of variant classifications between centres, and performing integrated genotype-phenotype analysis requires data sharing across geographic and trust-level boundaries, so that laboratories and clinicians can share and access relevant information. There are however continuing challenges to achieving high-quality and consistent data sharing across services[10]. Resolving these challenges requires:

- Acknowledging the need for data sharing to be conducted in the best interests of patients – to inform and accelerate their diagnoses
- A common standard and secure genotypic and phenotypic framework for sharing data which can integrate data from a variety of sources
- Clarity around the consent processes and legal framework to support this data sharing activity

Progressing these issues requires continued engagement with national initiatives including work by the National Data Guardian, to demonstrate the benefits and utility of data sharing for genomic diagnostics as well as mitigating against potential risks.

4. Next steps and action points

There was a clear consensus that the UK clinical genetics community should adopt the ACMG Guidelines for variant interpretation and classification, with agreement that there needs to be:

Refinement of the ACMG guidelines on a gene/disease basis

Harmonisation of classification schemes for all types of variants (SNV/indel, CNV and SV)

Harmonisation of results reporting processes including terminology

Training and EQA to support guideline adoption and dissemination of good practice

Close interaction with the international initiatives such as ClinGen/ACMG and alignment where appropriate with developing international standards

Engagement with other clinical specialities to address challenges around test referrals, and interpretation and reporting of results

Mechanisms, tools, and knowledge/data sharing both to encourage consistent variant interpretations and to support MDT working

Ongoing evidence collection and comparative analysis (e.g. through EQA) to evaluate and demonstrate improvements in outcomes arising from the above approaches

The main actions arising from this meeting are summarised below:

Action: **Confirm UK adoption** of ACMG framework

Lead: ACGS and BSGM

When/ how: Complete - statement released 15th November 2016

Action: **Develop EQA** for variant interpretations based on the ACMG framework

Lead: NEQAS

When: 2017

Action: **Engage with mainstream clinicians:** Via PHGF network of mainstreaming clinical champions to explore challenges around mainstream referrals and reporting

Lead: PHG Foundation

When/ how: Workshop - held on 29 March 2017

Action: **Provide updates on developments and progress** regarding the Guidelines - through professional and scientific meetings, and other relevant opportunities.

Share experience and review progress on UK implementation of the Guidelines

Lead: ACGS, BSGM, DECIPHER

When/ how: ACGS and BSMG annual meetings – 2017

ClinGen/DECIPHER – Curating the Clinical Genome conference – 2017

Action: **Undertake training** to support use of the ACMG framework, including train the trainer events:

- Initial training workshop to involve EQA exercises and contributions from laboratories of worked examples of ACMG-based variant interpretations
- Follow-up training – to support continued adoption and further help identify UK based issues to implementation

Lead: ACGS, with HEE support

When/ how: Workshop - held on 28th February 2017
Monthly multidisciplinary teleconferences from April 2017

Action: **Support further guideline development** with ClinGen and ACMG via distributed variant data analyses. To include testing of the ACMG structural variant guidelines

Lead: ACGS

When: Ongoing

Action: **Develop unified UK best practice interpretation guidelines** derived from ACMG framework and refined based on UK clinical service framework

Lead: ACGS

When: 2017

5. Appendix

5.1. Workshop organising committee

Dominic McMullan	Chair – Association Clinical Genomic Science (ACGS)
Professor Sian Ellard	Consultant Clinical Scientist - Royal Devon & Exeter NHS Foundation Trust
Sian Morgan	Chair – ACGS Quality Committee
Dr Helen Firth	Clinical Lead - DECIPHER
Professor William Newman	Chair – British Society for Genetic Medicine (BSGM)
Dr Caroline Wright	Programme Manager for the DDD Project
Dr Emma Baple	Clinical Lead for Rare Disease Validation and Feedback - Genomics England
Dr Stephen Abbs	Chair – UK NEQAS Steering Committee
Dr Richard Scott	Clinical Lead for Rare Diseases - Genomics England

5.2. Workshop participants

The Variant Classification and Interpretation workshop on 4 November 2016 was attended by 70 delegates representing most Regional Genetics services (laboratory and clinical teams) with additional invited representation from all BSGM constituent groups, NHSE (Genomics Implementation Unit), Genomics England, UK NEQAS, UKGTN, DECIPHER/DDD, HEE (Genomics Education Programme) and the PHG Foundation.

5.3. Invited presentations

Theme	Presenter	Presentation subject
Experiences in implementing and applying the ACMG Guidelines	**Dr Stephen Abbs** – UK NEQAS Steering Committee Chair	NEQAS variant classification experiences
	Professor Sian Ellard – Consultant Clinical Scientist, Royal Devon & Exeter NHS Foundation Trust. With contributions from Dr Emma Baple – Consultant Clinical Geneticist, Royal Devon & Exeter NHS Foundation Trust	Implementing ACMG Guidelines into a diagnostic lab – the Exeter experience
	Sirisha Hesketh – Clinical bioinformatician, Oxford Regional Genetics Laboratories	Oxford Regional Genetics Laboratory – experiences to date using ACMG Guidelines
	Dr Diana Eccles – Consultant Clinical Geneticist, University Hospital Southampton	Application in inherited cancer predisposition
Building on the ACMG Guidelines	**Dominic McMullan** – Chair ACGS and Consultant Clinical Scientist, West Midlands Regional Genetics Laboratory	Aligning CNV classifications to SNV classifications
	Dr Helen Firth – Consultant Clinical Geneticist, Cambridge University Hospitals NHS Foundation Trust and Honorary Faculty Member Wellcome Trust Sanger Institute	Integrating phenotype and clinical interpretation into classifications

5.4. Pre-workshop survey (1st of November 2016)

1. **Are you completing this as scientist or clinician for your centre?**
   Lab: 79% ;
   Clinician: 18%;
   Other: 3%;
   [Total responses: 33]

2. **How does your laboratory currently classify sequence variants?**
   ACGS guidelines: 74%;
   ACMG Guidelines: 0%;
   In-house classification: 6%;
   Combination of previous: 19%;
   [Total responses: 31]

3. **Has your laboratory implemented or is planning to implement ACMG** Guidelines **for sequence variant classification (Richards, 2015)?**
   Yes implementing: 10%;
   Yes planning: 17%;
   No and not planning: 10%;
   Undecided 63%;
   [Total responses: 30]

4. **For large panel and exomes do you classify variants before clinical reporting in following ways?**
   Mainly by laboratory and clinical scientists alone: 48%;
   Always as part of a MDT: 15%;
   Mixture of laboratory and MDT: 37%;
   [Total responses: 27]

5. **Do you think phenotypic data should be used in overall variant classification?**
   No: classification is at the variant level alone and contribution to phenotype is a clinical judgement: 3%;
   No: classification is at the variant level alone but a separate framework could be developed to rank contribution to phenotype: 9%;
   Occasionally, depending on the referral reasons and strength of phenotype: 47%;
   Always: the framework should be developed to include phenotypic evidence as part of the overall classification: 41%;
   [Total responses: 32]

6. **Have you followed ACMG and HGVS recommendations for removing the use of the word 'mutation' and replaced with 'pathogenic variant' in descriptions of internal findings on clinical reports?**
   No- do not agree with this: 32%;
   No- but mainly due to logistical challenges to doing this: 25%;
   Yes- doing or planning this now: 36%;
   Use of mutation is used only for describing *de novo* variants: 7%;
   [Total responses: 28]

5.5. Abbreviations

Acronym	Meaning
ACGS	Association for Clinical Genomics Science
ACMG	American College of Medical Genetics and Genomics
AMP	Association for Molecular Pathology
BSGM	British Society for Genetic Medicine
ClinGen	Clinical Genome [Resource]
CNV	Copy Number Variation
DDD	Deciphering Developmental Disorders
DECIPHER	DatabasE of genomiC variation and Phenotype in Humans using Ensembl Resources
EQA	External Quality Assessment
GeCIP	Genomics England Clinical Interpretation Partnership
HEE	Health Education England
HGVS	Human Genome Variation Society
indels	Insertion or deletion of bases
MDT	Multidisciplinary Team

NHSE	National Health Service England
NCBI	National Center for Biotechnology Information
PHE	Public Health England
SNV	Single Nucleotide Variation
SV	Structural Variant
UKGTN	UK Genetic Testing Network
UKNEQAS	UK National External Quality Assessment Service
VUS	Variant of Uncertain Significance

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About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.

About the ACGS

The Association for Clinical Genomic Science (ACGS) was established in 2012 from a merger of the Association for Clinical Cytogenetics and the Clinical Molecular Genetics Society with the vision of bringing together scientists working within genetics into one professional association. It is the largest of the constituent groups of the British Society of Genetic Medicine (BSGM).

Our members are professionals working within clinical genetic science and include scientists, technologists and bioinformaticians. We aim to promote, protect and preserve the good health of the patients we serve, by the promotion, encouragement and advancement of the study and practice of clinical genetic science. We develop and promote standards in clinical genetic science to ensure best practice. We also support the advancement of education, research and innovation in clinical genetic science.

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CAMBRIDGE UNIVERSITY
Health Partners
Knowledge-based healthcare

PHG Foundation
2 Worts Causeway
Cambridge
CB1 8RN
T +44 (0) 1223 761 900
www.phgfoundation.org

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